# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/334,325 | 06/16/1999 | STEWART A. CEDERHOLM-WILLIAMS | CV0276A | 5209 |

7590 07/27/2005

T R FURMAN
BRISTOL-MYERS SQUIBB COMPANY
100 HEADQUARTERS PARK DRIVE
SKILLMAN, NJ 08558

| EXAMINER | |
|---|---|
| CHEN, SHIN LIN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |

DATE MAILED: 07/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/334,325 | CEDERHOLM-WILLIAMS, STEWART A. | |
| | Examiner | Art Unit | |
| | Shin-Lin Chen | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 13-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

An appeal conference was held with SPE Nguyen and SPE Shukla on 7-18-05. Upon further consideration of the instantly claimed invention and for the completeness of the office action pertaining to 112 first and second paragraph, the finality of the Official action mailed 12-3-04 has been withdrawn and a new non-final office action is set forth below.

1. In view of the appeal brief filed on 5-5-05, PROSECUTION IS HEREBY REOPENED. A new ground of rejection is set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Claims 1 and 13-16 are pending and under consideration.

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1 and 13-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1 and 13-16 are directed to a method of transforming a cell *in vitro* or *in vivo* by applying, in order, a nucleic acid, such as a plasmid or the nucleic acid is incorporated in a virus, to the cell, a pliable and adhesive fibrin gel to the cell so a to entrap a transformation effective amount of the nucleic acid in the fibrin gel adhered to the cell. Claim 15 specifies the pliable, adhesive fibrin gel is formed by mixing a fibrin monomer composition with a polymerizing agent and the cell is contacted with the mixture while the mixture is pliable and adhesive. Claim 16 specifies the fibrin monomer composition comprises acid-solubilized fibrin and the polymerizing agent comprises a base effective to neutralize the mixture to form fibrin polymer.

The specification discusses advantages of fibrin monomer-based sealants over fibrinogen-based sealants and discloses the preparation of preferred sealant compositions and the incorporation of nucleic acid into fibrin gel, and spraying of transforming composition comprising nucleic acids, fibrin monomer preparation, and polymerizing agent to site of delivery so that these three components can converge and mix. The claims are directed to a method of transforming a cell *in vitro* and *in vivo* via various administration routes. The claims read on applying a nucleic acid to a cell first and then applying a pliable, adhesive fibrin gel to said cell so as to transform the cell *in vivo* at any location of any subject including human beings, mammals, fishes, birds, insects, fungus, plants etc., via various administration routes.

The specification fails to provide adequate guidance and evidence for transforming a cell *in vitro* or *in vivo* by applying a nucleic acid, such as a vector or a virus carrying the nucleic acid, to the cell first and then applying a pliable, adhesive fibrin gel to said cell so as to transform the cell *in vitro* or *in vivo* at any location of any subject via various administration routes. The specification merely states that "the TC can be applied to cells or tissue, and the sealant can be applied to fix the TC in place" (see specification, p. 17, lines 28-29). No working example or evidence has been provided in the specification in regard to how the cells are transformed by the claimed method and whether the cells are transformed *in vitro* or *in vivo* via various administration routes. The mechanism of the cell transformation by the claimed method was unknown at the time of the invention.

The specification teaches compositions of fibrin sealants that incorporate recombinant vectors for delivery to a tissue or cell, and "[B]y use of such compositions, the vectors can be maintained at a locally at high concentration in the solid gel produced by the sealant, thereby increasing the efficiency of transfection or transformation of cells (see specification, p. 2, lines 9-13). The orderly method steps of (1) applying a nucleic acid to the cell and then (2) adhering a pliable, adhesive fibrin gel to the cell so as to entrap a transformation effective amount of nucleic acid in the fibrin gel adhered to the cell as instantly claimed, must provide such a high concentration of the vector in order to increase the efficiency of the transformation of the cells *in vitro* or *in vivo* in the claimed invention. The state of the art of using fibrin gel for delivering nucleic acid is such that the nucleic acid solution is mixed with fibrin monomer or fibrinogen first, then the fibrin gel is polymerized before being delivered to the target site. Donovan, 1998 (US Patent No. 5,833,651) constructs plasmid CMVhpAP expressing the reporter hpAP gene

under the control of CMV promoter and an E1 deleted recombinant adenoviral vector ADVhpAP expressing hpAp, and prepared a fibrin covered stent which was placed in a solution of plasmid or virus overnight to load the plasmid or virus into the fibrin covered stent for determining whether fibrin enhances gene delivery to the artery (e.g. column 18, 19, 20). Donovan further teaches mixing a solution of fibrin monomer and virus containing nucleic acid to form a polymer, i.e. fibrin gel, which can be used to deliver the virus to the cell (e.g. column 13). Schek et al., 2003 (Molecular Therapy, Vol. 9, No. 1, p. 130-138) teaches mixing adenoviral particles with fibrinogen solution in vitro, gelation of the fibrinogen by adding thrombin to form hydrogel, and implanting the hydrogel to immunocompromised mice (e.g. p. 137, left column). Schek shows that fibrin hydrogel exhibits a threefold extension of bioactivity of the virus delivered as compared to virus without hydrogel and suggests hydrogel may be used as carrier to control delivery of the virus and resultant tissue regeneration (e.g. abstract). In other words, the art of record only teaches pre-mixing fibrin with nucleic acid resulting in the nucleic acid being trapped in the fibrin gel for the method to work. The specification as filed also teaches the same (see p. 2, lines 9-13, p. 17, lines 8-17, lines 27-28). Therefore, neither the art nor the specification teaches where the nucleic acid is first applied to the cells followed by application of fibrin so as to transform cells with increased transformation efficiency. There is no evidence of record that shows increased or enhanced efficiency of cell transformation by the claimed method either in vitro or in vivo via various administration routes. When the nucleic acid is first applied to the cells followed by application of fibrin, the specification fails to provide any specific guidance as to how one skilled artisan would have first applied nucleic acid to the cells and subsequently applied fibrin in vitro or in vivo to the same cells so as to trap effective amount of

nucleic acid to transform the cells with said nucleic acid. Since the mechanism of cell transformation by the claimed method was unknown at the time of the invention and the lack of working example and evidence of record regarding the claimed method, one skilled in the art would not know how to increase or enhance the efficiency of cell transformation *in vitro* or *in vivo* by using the claimed method and would require undue experimentation to practice over the full scope of the invention claimed.

Further, the claims encompass transforming cells in vivo via various administration routes, such as intravenous administration, intraperitoneal administration, oral administration, subcutaneous administration, and intramuscular administration etc. The specification fails to provide adequate guidance and evidence for how to apply nucleic acid to the cell first and then administer a pliable, adhesive fibrin gel to the cells at various locations of a subject via various administration routes such that the cells at the target site of the subject would have increased or enhanced transformation efficiency as compared to other method, such as the method known in the art by mixing the nucleic acid solution and the fibrin monomer together before administration to the cells. The specification fails to demonstrate how intravenous administration, oral administration, intraperitoneal administration or subcutaneous administration could deliver the pliable, adhesive fibrin gel to the cells of kidney, pancreas, heart, stomach, colon, liver, intestine, or brain and the pliable, adhesive fibrin gel would not polymerize before reaching the target cells in vivo. The lack of teachings and evidence of record for such delivery of the pliable, adhesive fibrin gel in vivo would require one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

The specification also fails to provide adequate guidance and evidence for how to administer a pliable, adhesive fibrin gel to a cell having administered nucleic acid in a subject such that target cells in said subject are transformed with said nucleic acid. The specification fails to provide adequate guidance for how to deliver the pliable, adhesive fibrin gel before the fibrin gel is polymerized to target cells in a subject via various administration routes for transformation of said cells with increased efficiency. It was known in the art that the pliable, adhesive fibrin gel will polymerize quickly. The specification states that "Generally, the sealant mixture remains conveniently pliable for about 30 seconds or less"(page 17, lines 16, 17). Since the pliable, adhesive fibrin gel will polymerize in a short period of time, one would need to deliver said fibrin gel to target cells at various locations in a subject before polymerization of said fibrin gel so as to increase transform efficiency of said target cells with a nucleic acid. This would be problematic because there is not much time for one skilled in the art to deliver the pliable and adhesive fibrin gel to the target cells inside the body of the subject, such as cells in liver, kidney, pancreas, heart, colon, intestine, stomach etc, before the pliable and adhesive fibrin gel is polymerized. When the pliable and adhesive fibrin gel is polymerized before it reaches the target cells, the nucleic acid on the cells would not be entrapped in the fibrin gel and the target cells would not be transformed with said nucleic acid or with increased transformation efficiency as compared to other methods, such as mixing the nucleic acid and the fibrin monomer before administration. There is no evidence of record that shows transformation of target cells increased transformation efficiency of target cells in a subject with any nucleic acid via administering the nucleic acid to the cells first and then administering the pliable and adhesive fibrin gel to said cells.

The claims read on applying a nucleic acid to cells in vivo so as to transform cells and the transformation of cells in vivo must have a use, which is to provide therapeutic effect in vivo. The title of the present invention reads "Fibrin sealant as a transfection /transformation vehicle for gene therapy". Therefore, the claims read on gene therapy in vivo. The state of the art for gene therapy *in vivo* was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate resolution of the problem of vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression...The use of viruses (viral vectors) is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells, However, humans

have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses." (e.g. p. 239, column 3).

Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract).. These arts emphasize the unpredictability of the state of the art of gene therapy in general and in view of the lack of any specific guidance and evidence in the specification as to how to deliver nucleic acid and fibrin to the same cell in sufficient amounts so as to increase transformation efficiency, when the nucleic acid is applied first followed by fibrin a skiled artisan would have required extensive experimentation to practice over the full scope of the invention claimed. In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to transform a cell *in vivo* with any nucleic acid and a pliable,

adhesive fibrin gel via various administration routes so as to provide therapeutic effects in an individual for a particular disease or disorder.

The quantity of experimentation needed to make or use the present invention includes trail and error experimentation to elucidate the mechanism of cell transformation *in vitro* or *in vivo* by applying nucleic acid to cells first, then administering a pliable, adhesive fibrin gel to said cells, trial and error experimentation to determine how to increase or enhance cell transformation efficiency *in vitro* and *in vivo* by the claimed method, trial and error experimentation to determine how to administer a nucleic acid to the target cell on the surface of a subject or to the target cell at various locations inside the body of a subject, such as liver, kidney, lung, intestine, stomach etc., trial and error experimentation to determine how to administer the pliable and adhesive fibrin gel to the target cell on the surface of a subject or to the target cell at various locations inside the body of a subject, such as liver, kidney, lung, intestine, stomach etc., via various administration routes before the fibrin gel get polymerized so as to transform the target cell with said nucleic acid or to increase cell transformation efficiency, and trial and error experimentation to transform target cells with the claimed method such that therapeutic effects can be obtained for a particular disease or disorder *in vivo*.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of ordinary skill which is high, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Applicant argues that the specification teaches how to make the transforming composition and that transforming nucleic acids are well-known, cell transformation *in vitro* is enabled, and one of ordinary skill knows how to measure transformation (brief, page 4). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph rejection.

Applicant argues that the 35 U.S.C. 112 first paragraph enablement rejection is related to 35 U.S.C. 101 rejection and the Office does not follow the Utility Examination Guidelines (brief, pages 4-6). This is not found persuasive because the 35 U.S.C. 112 first paragraph enablement rejection is **not** a 35 U.S.C. 101 rejection. Applicant fails to provide arguments directed to the 35 U.S.C. 112 first paragraph enablement rejection. Applicant's argument regarding the 35 U.S.C. 101 rejection is irrelevant to the 35 U.S.C. 112 first paragraph rejection. The claimed invention is not enabled for the reasons set forth above under 35 U.S.C. 112 first paragraph rejection.

***Claim Rejections - 35 USC § 112***

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1 and 13-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "a transformation effective amount of a nucleic acid" in line 2 and the phrase "a transformation effective amount of the nucleic acid" in lines 3-4 of claim 1 are vague and

render the claim indefinite. It is unclear whether "a transformation effective amount of a nucleic acid" in line 2 is the same transformation effective amount of nucleic acid as or different from "a transformation effective amount of the nucleic acid" in lines 3-4. Claims 13-16 depend from claim 1 but fail to clarify the indefiniteness.

The phrase "transforming the cell with the nucleic acid" in line 5 of claim 1 is vague and renders the claim indefinite. It is unclear whether "transforming the cell with the nucleic acid" in line 5 is meant to be a third step of the claimed method independent of the first two steps or a conclusion referring back to the preamble of the method, i. e. the cell is transformed. Claims 13-16 depend from claim 1 but fail to clarify the indefiniteness.

## *Conclusion*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the

USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER

SHIN-LIN CHEN
PRIMARY EXAMINER

Supervisory Patent Examiner
AU 1633